UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,145	04/16/2001	Benjamin F. Cravatt	SCRIP1210-3	7817

7590 09/09/2005

Lisa A. Haile, Ph.D.
Gray Cary Ware & Freidenrich LLP
Suite 1600
4365 Executive Drive
San Diego, CA 92121-2189

EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 09/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,145	CRAVATT ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14,16,18,21-24 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14,16,18, 21, 22 and 24* is/are rejected.

7)☐ Claim(s) *23 and 26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

200

DETAILED ACTION

Status of the Application

1. The Response filed April 25, 2005 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 12, 14, 16-18 and 21-24 were pending. Applicants amended claims 12, 14 and 24. In addition, Applicants canceled claim 17 and added claim 26. Therefore, claims 12, 14, 16, 18, 21-24 and 26 are examined on the merits.

Withdrawn Objections/Rejections

4. All previous rejections and/or objections are withdrawn.

New Rejections

Claims Rejections - 35 U.S.C. 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

5. Claims 24 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

Claim(s) 24 was amended in the 4/25/05 Response. However, the Examiner cannot find support for the current "Z" moiety as amended. Specifically, the current amendment sets for a Z moiety that contains a terminal "CH_3" group. This appears to be in error (e.g., see 35 U.S.C. 112, second paragraph rejection below). Figure 10 (see specification) only provides for "one" R group substitution i.e., SO_2-O-R. However, Applicants' interpretation of figure 10 would require "two" R group substitutions (i.e., the SO_2-O underlined oxygen cannot bind both the "CH_3" and "linker-Biotin" groups simultaneously). Thus, to the extent that Applicant claims now read on SO_2-$O^+(CH_3)$-linker biotin (or some other variation wherein the CH_3 is substituted at some other unspecified point) instead of SO_2-O-linker biotin, this change in scope constitutes new matter. If applicant believes this rejection is in error, applicant must disclose where in the specification support for this amendment can be found in accordance with MPEP 714.02.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claim 24**, the "Z" moiety is vague and indefinite because it appears that Applicants' sulfonates 1-11 are somehow substituted between the "CH_3" group and the rest of the molecule (i.e., the biotin-linker). However, only one "Z" substitution is available on Sulfonates 1-11 (i.e., the R-SO_2-O- underlined oxygen cannot have two bind two groups, the -CH_3 and -linker-Biotin substituents, simultaneously)? Applicants are requested to clarify and/or correct. Therefore, the metes and bounds of the claimed invention cannot be determined.

Claims Rejections - 35 U.S.C. 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 12, 14, 16, 18, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (U.S. Patent No. 6,852,544 B2) and Purohit et al. (Purohit, A.; Williams, G. J.; Howarth, N. M.; Potter, B. V. L.; Reed, M. J. "Inactivation of Steroid Sulfatase by an Active Site-Directed Inhibitor, Estrone-3-O-Sulfamate" *Biochemistry* **1995**, *34*, 11508-11514) as evidenced by Luppa et al. (Luppa, P.; Hauck, S.; Schwab, I.; Birkmayer, C.; Hauptmann, H. "6α-Biotinylated Estrone: Novel Tracer in Competitive Chemiluminescence Immunoassay of Estrone in Serum" *Clin. Chem.* **1995**, *41(4)*, 564-570) (of record) and as evidenced by Alcock (Alcock, S. "SENSPOL: European Network on Sensors for Monitoring Water Pollution" *European Union Thematic Network Newsletter* **2002**, *6*, 1-29) (of record). Please note: MPEP 2131.01(d) permits the citation of references or evidence in order to show that a characteristic not disclosed in the reference is inherent.

For ***claim 12***, Aebersold et al. (see entire document) teach a method for the rapid quantitative analysis of proteins or protein function in complex mixtures (e.g., see title and abstract), which reads on the claimed invention. For example, Aebersold et al. teach a method for screening for molecules having an affinity for an active protein in a complex mixture of proteins from a biological source (e.g., see Summary of Invention, column 3, second full paragraph, "...the methods herein can be employed to screen for changes in the expression or state of enzymatic activity [e.g., an active protein] of specific proteins"; see also third full paragraph, "The methods herein can also be used to implement a variety of clinical and diagnostic analyses to detect the presence, absence, deficiency or excess of a given protein or protein function in a biological fluid (e.g., blood), or in cells or tissue [i.e., a biological source]. The method is particularly useful in

the analysis of complex mixtures of proteins"). Aebersold et al. also disclose the use of a combinatorial chemical library comprising a mixture of members (e.g., see column 5, second to last paragraph, "One or more affinity labeled reagents with different PRG groups [i.e., a library of affinity labeled reagents with different PRG groups] are introduced into a mixture containing proteins and the reagents react with certain proteins to tag them with the affinity label"; see also column 3, third full paragraph, "In general, the affinity labeled protein reactive reagents of this invention have three portions: an affinity label (A) covalently linked to a protein reactive group (PRG) through a linker group (L): A-L-PRG").

In addition, Aebersold et al. disclose **(1)** combining said combinatorial chemical library with said complex mixture of proteins, in an active form and inactivated form, under conditions for reaction of said sulfonyl functional group with active proteins to form a conjugate (e.g., see column 5, second to last paragraph, "One or more affinity labeled reagents with different PRG groups [i.e., a library] are introduced into a mixture containing proteins [i.e., the library is "combined" with the proteins] and the reagents react with certain proteins to tag them [i.e., formation of a conjugate] with the affinity label"; see also column 4, lines 25-36, "Two types of PRG groups are specifically provided herein: (a) those groups that selectively react with a protein functional group to form a covalent or non-covalent bond tagging the protein at specific sites [i.e., a conjugate]"). Aebersold et al. also disclose the use and comparison of both active and inactive proteins (e.g., see paragraph bridging column 5-6, "In this method, each sample to be compared [i.e., active and inactive] is treated with a different isotopically labeled

reagent to tag certain proteins therein with the affinity label"; see also column 1, last full paragraph, "Furthermore, the activity of proteins [i.e., active versus inactive] is frequently modulated by post-translational modifications, in particular protein phosphorylation, and dependent on the association of the protein with other molecules including DNA and proteins ... It is therefore essential that a complete description of a biological system include measurements that indicate the identity, quantity and the state of activity of the proteins which constitute the system"; see also column 3, first full paragraph, "The method can also be employed to screen for and identify proteins whose expression level in cells, tissue or biological fluids is affected by ... a change in condition or cell state (e.g., disease state, malignancy, site-directed mutation, gene knockouts) of the cell ... For example, comparisons of protein expression profiles of normal [inactive for malignancy] and malignant cells [active for malignancy] can result in the identification of proteins whose presence or absence is characteristic and diagnostic of the malignancy"; see also column 6, last full paragraph wherein screening a "state of modification" is disclosed; see especially column 6, last paragraph, "... the invention provides a MS method for detection of the presence [i.e., active] or absence [i.e., inactive] of a protein function, e.g., an enzyme activity, in a sample). Aebersold et al. also disclose **(2-3)** isolating conjugates from said active and inactivated complex mixture of proteins and comparing conjugates formed from with said active and inactivated complex mixture of proteins whereby conjugates in said active complex mixture absent in said inactivated complex mixtures are comprised only of active proteins reactive with members of said chemical combinatorial library (e.g., see column 3, last full paragraph, "The inventive method

employs affinity-labeled protein reactive reagents that allow for the selective isolation of peptide fragments or the products of reaction with a given protein (e.g., products of enzymatic reaction) from complex mixtures. The isolated peptide fragments or reaction products are characteristic of the presence of a protein or the presence of a protein function, e.g., an enzymatic activity, respectively, in those mixtures. Isolated peptides or reaction products are characterized by mass spectrometric (MS) techniques"; see also column 3, first full paragraph, "In this method, each sample to be compared is treated with a different isotopically labeled reagent to tag certain proteins therein with the affinity label. The treated samples are then combined, preferably in equal amounts, and the proteins in the combined sample are enzymatically digested, if necessary, to generate peptides. Some of the peptides are affinity tagged [e.g., form conjugates] and in addition tagged peptides originating from different samples are differentially isotopically labeled").

For ***claim 18***, Aebersold et al. disclose biotin (e.g., see Aebersold et al., claim 10).

For ***claims 21 and 22***, Aebersold et al. disclose sulfonate (e.g., see Aebersold et al., "Thiol reactive groups include ... sulfonated alkyl").

The prior art teachings of Aebersold et al. differ from the claimed invention as follows:

For ***claim 12***, Aebersold et al. are deficient in that they do not specifically teach the use of a library of reagents comprising a mixture wherein the mixture includes a plurality of members with the formula R*(F-L)-X.

However, Purohit et al. teach the following limitations that are deficient in Aebersold et al.:

For ***claims 12 and 14***, Purohit et al. (see entire document) disclose a combinatorial chemical library of R*(F-L)-X compounds wherein the X group is "estrone", the L group is a "bond", the F group is "SO_2" [i.e., a sulfonyl group] and the R group varies in the library to include "NH_2, NHMe, NMe_2, H or Me" (e.g., see Purohit et al., figure 1, compounds 2 and 4-6). Purohit et al. do not explicitly state that the estrone portion of the molecule has the ability to act as a "hapten" i.e., has the ability to elicit an immune response (e.g., see newly amended claims 12 and 14 wherein "X is a ligand selected from a group consisting of ... and hapten"). However, the Examiner contends that the estrone disclosed in Purohit et al. would inherently possess this activity as evidenced by Luppa et al. and Alcock (e.g., see Luppa et al., abstract which shows that estrone can act as a hapten for use in competitive chemiluminescence immunoassays for estrone in serum; compare also compound Bio-E1 in figure 1 of Luppa et al. to compounds (1)-(6) in figure 1 of Purohit et al.; see also figures in Luppa et al.; see also Alcock, page 16, "Spotted transducer" section wherein estrone is again disclosed as a hapten, "... each polymer-hapten conjugate (atrazine, estrone and isoproturon [are the haptens]) ..."). If the prior art structure is capable of performing the intended use, then it meets the claim. The Office does not have the facilities to make a comparison and the burden is on the applicants to establish any difference between the transducing elements of the art and the instant claims. Se In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Here,

both Luppa et al. and Alcock clearly demonstrate that estrone has the capability of performing the intended use (i.e., ability to act as a hapten).

For ***claim 16***, Purohit et al. disclose library members with different on-rates (see page 11510, Results, "Nature of EMATE Inhibition of Sulfatase Activity" section, especially column 2, paragraph 4).

For ***claim 21***, Purohit et al. disclose F = sulfamate (see Purohit et al., page 11508, figure 1, compound 6).

It would have been *prima facie* obvious to one skilled in the art at the time the invention was made to use the library of steroid sulfatase inhibitors disclosed by Purohit et al. as the "PRG" portion of the affinity tags as disclosed by Aebersold et al. because Aebersold et al. explicitly state that the PRG groups just need to "... selectively react with a protein functional group to form a covalent ... bond [for] tagging the protein at specific sites" (e.g., see Aebersold et al., column 4, lines 25-36), which would encompass the covalent tagging of the steroid sulfatase proteins disclosed by Purohit et al. (e.g., see figure 8; see also , "PRG groups can also be substrates for a selected enzyme of interest. The enzyme of interest may, for example, be one that is associated with a disease state [i.e., steroid sulfatase is associated with many disease states involved in the regulation and synthesis of estrogenic steroids]"). Furthermore, one of ordinary skill in the art would have been motivated to use library members that interact with steroid sulfatase because Aebersold et al. explicitly state that library members that react with "steroid sulfatase" is a preferred embodiment (e.g., Aebersold et al., Column 49, Table IV, "Steroid Sulfatase deficiency" entry wherein 3β-hydroxyl steroid sulfatase is explicitly

disclosed; see also column 23, paragraph 2, "Table 4 provides exemplary enzymes that are associates with certain birth defects or disease states. These enzymes can be assayed by the methods described herein"; see also Table IV, "Hunter Syndrome). Furthermore, Purohit et al. state, "The development of an active site-directed irreversible inhibitor of steroid sulfatase activity will allow the roles that these enzymes have in a number of physiological and pathological processes to be evaluated" (e.g., see Purohit et al., abstract), which encompasses the physiological screening of medically related enzymes including steroid sulfatase as disclosed by Aebersold et al. (Table IV). Finally, one of ordinary skill in the art would have reasonably expected to be successful because Aebersold et al. explicitly state that 3β-hydroxyl steroid sulfatase enzymes can be screened (e.g., see Table IV), which is exactly what is disclosed by Purohit et al. (see Purohit et al., abstract). In addition, Purohit et al. teach that their library members can interact with the target protein in complex mixtures such as (e.g., the placental microsomes and intact MCF-7 breast cancer cells that contain estrone sulfatase and dehydroepiandrosterone sulfatase) wherein conjugates are formed between the library members and the sulfatase proteins (see Purohit et al., page 11513, figure 8; see also Materials and Methods section). In addition, Purohit et al. disclose isolating said conjugates from the active and inactive complex mixture (e.g., see Purohit et al., page 11509, column 2, paragraph 1). Aebersold et al. further state that mass spectrometry "... has reached a level of sensitivity which now permits the identification of essentially any protein" (e.g., see Aebersold et al., Background of Invention), which would include the sulfatase disclosed by Purohit et al.

Allowable Subject Matter

10. Claims 23 and 26 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

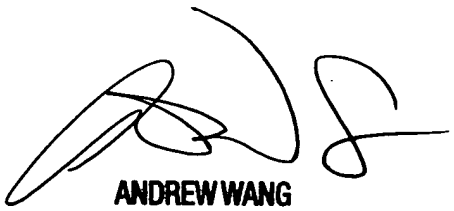
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
August 31, 2005



ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600